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(54) Title: FORMULATIONS

(57) Abstract

The invention relates to pharmaceutically stable oxaliplatin solution formulations, to the method of use thereof in the treatment of cancer tumors, to processes for the preparation of such formulations, and to a method for stabilizing solutions of oxaliplatin.

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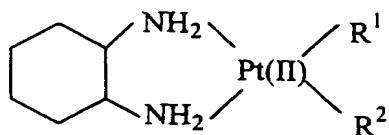
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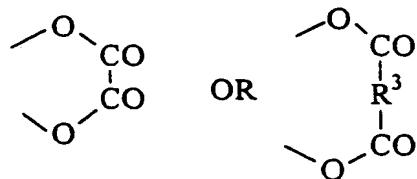
## FORMULATIONS

The invention relates to pharmaceutically stable oxaliplatin solution formulations, to the method of use thereof in the treatment of cancer tumors, to processes for the preparation of such formulations and to a method for stabilizing solutions of oxaliplatin.

5 Kidani et al., U.S. Patent No. 4,169,846, issued October 2, 1979, disclose cis-platinum(II) complexes of isomers (cis-, trans-d, and trans-l isomers) of 1,2-diaminocyclohexane represented by the general formula



wherein the stereoisomerism of 1,2-diaminocyclohexane is cis, trans-d, or trans-l; and R<sup>1</sup> and 10 R<sup>2</sup> represent halogen atoms, or R<sup>1</sup> and R<sup>2</sup> may, when taken together, form a group represented by the formula:



15 where R<sup>3</sup> represents a >CH<sub>2</sub> group, a >CHCH<sub>3</sub>, or >CHCH<sub>2</sub>CH<sub>3</sub> group. Cis-oxalato(trans-l-1,2-diaminocyclohexane)platinum (II) is specifically disclosed as example 4(i). The compounds are stated to possess anti-tumor activity.

Okamoto et al., U.S. Patent No. 5,290,961, issued March 1, 1994, disclose a process for preparing various platinum compounds including cis-oxalato(trans-l-1,2-cyclohexanediamine)platinum (II). A similar disclosure is found in EP 617043, published September 28, 1994.

20 Tozawa et al., U.S. Patent No. 5,298,642, issued March 29, 1994, disclose a process for optically resolving optically active platinum compounds by the use of chiral high

5 perfomance liquid chromatography. The resolution of cis-oxalato(trans-1 and trans-1,2-cyclohexane-diamine)platinum (II) is specifically disclosed. Nakanishi et al., U.S. Patent No. 5,338,874, issued August 16, 1994, disclose optically pure cis-oxalato(trans-1,2-cyclohexanediamine)platinum (II) and methods of preparing the same. A similar disclosure is found in EP 567438, published October 27, 1993.

Okamoto et al., U.S. Patent No. 5,420,319, issued May 30, 1995, disclose cis-oxalato(trans-1,2-cyclohexanediamine)platinum(II) having high optical purity and a process for preparing the same. A similar disclosure is found in EP 625523, published November 23, 1994.

10 Masao et al., EP . 715854, published June 12, 1996, disclose a process of compatibly administering cis-oxalato(1R,2R-diaminocyclohexane)platinum(II), abbreviated as ("l-OHP"), with one or more existing carcinostatic substances and a carcinostatic substance comprising one or more compatible agents and l-OHP.

15 Kaplan et al., Canadian patent application No. 2,128,641, published February 12, 1995, disclose stable solutions of malonato platinum (II) antitumor agents, such as carboplatin, containing a stabilizing amount of 1,1-cyclobutanedicarboxylic acid or a salt thereof and a pharmaceutically acceptable carrier, said solution having a pH about 4 to about 8.

Ibrahim et al., WO94/12193, published June 9, 1994, disclose a composition for 20 jointly administering cisplatin and oxaliplatin, said composition being a freeze-dried composition containing cisplatin and oxaliplatin in a weight ratio of about 2:1 to 1:2 and a pharmaceutically acceptable chloride ion-free acidic buffer with a neutral substance being used as a ballast.

Tsurutani et al., EP 486998, published May 27, 1992, disclose a slow-releasing composition comprising a platinum-containing anticancer agent bound to deacetylated chitin. A similar disclosure is found in U.S. Patent No. 5,204,107, issued April 20, 1993.

Ibrahim et al., Australian patent application No. 29896/95, published March 7, 1996  
5 (a patent family member of WO 96/04904, published February 22, 1996), disclose a pharmaceutically stable preparation of oxaliplatin for parenteral administration consisting of a solution of oxaliplatin in water at a concentration in the range of 1 to 5 mg/mL and having a pH in the range of 4.5 to 6. A similar disclosure is found in U.S. Patent No. 5,716,988, issued February 10, 1998.

10 Johnson, U.S. Patent No. 5,633,016, issued May 27, 1997, discloses pharmaceutical compositions comprising a compound of the camptothecin analog class and a platinum coordination compound and a pharmaceutically acceptable carrier or diluent. A similar disclosure is found in WO93/09782, published May 27, 1993.

Bach et al., EP 393575, published October 24, 1990, disclose a combination therapy  
15 of therapeutically-effective amounts of a cytoprotective copolymer and one or more directly acting antineoplastic agents for the treatment of neoplastic disease.

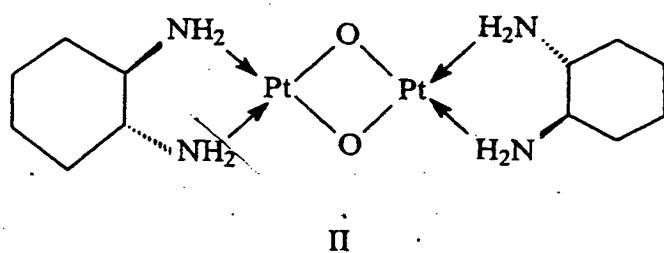
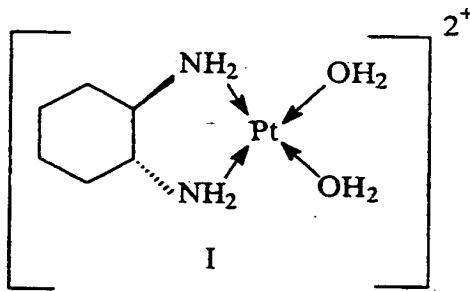
Nakanishi et al., EP 801070, published October 15, 1997, disclose a process for preparing various platinum complexes including cis-oxalato(trans-1,2-cyclohexanediamine)Pt(II).

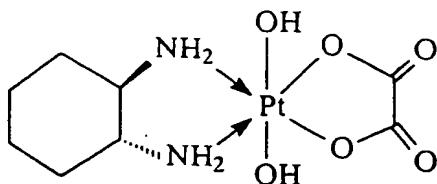
20 Oxaliplatin is currently available for both preclinical and clinical trials as a lyophilized powder which is reconstituted just before administration to a patient with water for injection or a 5% glucose solution, followed by dilution with a 5% glucose solution. Such a lyophilized product can, however, have several disadvantages. First of all, the lyophilization process can be relatively complicated and expensive to perform. In addition,  
25 the use of a lyophilized product requires that the product be reconstituted at the time of use,

which provides an opportunity for there to be an error in choosing the appropriate solution for the reconstitution. For instance, the mistaken use of a 0.9% NaCl solution, which is a very common solution for the reconstitution of lyophilized products or for the dilution of liquid preparations, in the reconstitution of a lyophilized oxaliplatin product would be detrimental to the active ingredient in that a rapid reaction would occur, resulting not only in the loss of oxaliplatin, but in the precipitation of the species produced. Other disadvantages of a lyophilized product are:

- (a) reconstitution of a lyophilized product increases the risk of microbial contamination over a sterile product which does not require reconstitution;
- 10 (b) there is a greater risk of sterility failure with a lyophilized product as compared to a solution product sterilized by filtration or by heat (terminal) sterilization; and
- (c) a lyophilized product has a potential for incomplete dissolution upon reconstitution resulting in particles which are undesirable for an injectable product.

It has been shown that in aqueous solutions oxaliplatin can, over time, degrade to produce as impurities varying amounts of diaquo DACH platin (formula I), diaquo





## III

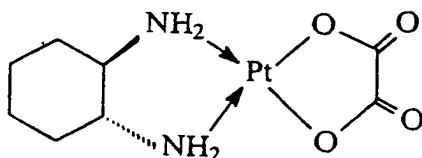
DACH platin dimer (formula II) and a platinum (IV) species (formula III). As the level of impurities present in any pharmaceutical formulation can, and in many cases does, affect the toxicological profile of the formulation, it would be desirable to develop a more stable 5 solution formulation of oxaliplatin which either does not produce the above-described impurities at all or which produces such impurities in significantly smaller quantities than has heretofore been known.

Accordingly, a need exists for solution formulations of oxaliplatin in a ready-to-use (RTU) form, which overcome the above-described disadvantages and which are 10 pharmaceutically stable over prolonged periods of storage, i.e., 2 years or more. It is accordingly an object of the present invention to overcome these disadvantages by providing a pharmaceutically stable oxaliplatin solution formulation in ready-to-use form.

More specifically, the present invention relates to a stable oxaliplatin solution formulation comprising oxaliplatin, an effective stabilizing amount of a buffering agent and a 15 pharmaceutically acceptable carrier.

Oxaliplatin, which is known chemically as *cis*-oxalato(*trans*-1,2-cyclohexanediamine)platinum (II) (can also be named as [SP-4-2]- (1*R*,2*R*)-(cyclohexane-1,2-diamine-*k*<sup>2</sup>*N,N'* (oxalato(2-)-*k*<sup>2</sup>*O*<sup>1</sup>,*O*<sup>2</sup>]*platinum* (II), (1,2-cyclohexanediamine-*N,N'*)[ethanedioato(2-)-*O,O'*]-[SP-4-2-(1*R*-*trans*)]-*platinum*, *cis*-[oxalato(1*R*,2*R*-cyclohexanediamine)*platinum* (II)], 20 [(1*R*,2*R*)-1,2-cyclohexanediamine-*N,N'*][oxalato(2-)-*O,O'*]*platinum*, [SP-4-2-(1*R*-*trans*)]- (1,2-cyclohexane-diamine-*N,N'*)[ethanedioato(2-)-*O,O'*]*platinum*, 1-OHP, and *cis*-

oxalato(trans-1,2-diaminocyclohexane(platinum (II)), and has the chemical structure shown below,



is a cytostatic antineoplastic agent which is useful in the therapeutic treatment of various  
5 types of susceptible cancers and tumors, such as, for example, colon cancer, ovarian cancer, epidermoid cancer, cancers of germinal cells (e.g., testicular, mediastina, pineal gland), non-small cell lung cancers, non-Hodgkins' lymphoma, breast cancer, cancers of the upper respiratory and digestive tracts, malignant melanoma, hepatocarcinoma, urothelial cancers, prostate cancers, small cell lung cancer, pancreatic cancer, gall bladder cancer, anal cancer,  
10 rectal cancer, bladder cancer, small intestine cancer, stomach cancer, leukemia and various other types of solid tumors.

The preparation, physical properties and beneficial pharmacological properties of oxaliplatin are described in, for example, U.S. Patents Nos. 4,169,846, 5,290,961, 5,298,642, -  
5,338,874, 5,420,319 and 5,716,988, European patent application No. 715854 and Australian  
15 patent application No. 29896/95, the entire contents of which are herein incorporated by reference.

Oxaliplatin is conveniently present in the formulations of the present invention in the amount of from about 1 to about 7 mg/mL, preferably in the amount of from about 1 to about 5 mg/mL, more preferably in the amount of from about 2 to about 5 mg/mL, and in particular  
20 in the amount of about 5 mg/mL.

The term buffering agent as used herein means any acidic or basic agent which is capable of stabilizing oxaliplatin solutions and thereby preventing or retarding the formation of unwanted impurities such as diaquo DACH platin and diaquo DACH platin dimer. The

term thus includes such agents as oxalic acid or alkali metal salts (e.g., lithium, sodium, potassium and the like) of oxalic acid, and the like or mixtures thereof. The buffering agent is preferably oxalic acid or sodium oxalate and most preferably is oxalic acid.

The buffering agent is present in the formulations of the present invention in an effective stabilizing amount. The buffering agent is conveniently present in a molar concentration in the range of from about  $5 \times 10^{-5}$  M to about  $1 \times 10^{-2}$  M, preferably in a molar concentration in the range of about  $5 \times 10^{-5}$  M to about  $5 \times 10^{-3}$  M, more preferably in a molar concentration in the range of from about  $5 \times 10^{-5}$  M to about  $2 \times 10^{-3}$  M, most preferably in a molar concentration in the range of from about  $1 \times 10^{-4}$  M to about  $2 \times 10^{-3}$  M, especially in a molar concentration in the range of from about  $1 \times 10^{-4}$  M to about  $5 \times 10^{-4}$  M, and in particular in a molar concentration of about  $2 \times 10^{-4}$  M or about  $4 \times 10^{-4}$  M.

The term pharmaceutically acceptable carrier as used herein refers to the various solvents which can be employed in the preparation of the oxaliplatin solution formulations of the present invention. In general, the carrier will be water, one or more other suitable solvents, or a mixture of water and one or more other suitable solvents. Preferably, the carrier will be either water or a mixture of water and one or more other suitable solvents, and more preferably, the carrier is water. The water that is used is preferably pure water, i.e., sterile water for injection. Representative examples of the other suitable carriers (solvents) which can be utilized according to the present invention include polyalkylene glycols, such as polyethylene glycol, polypropylene glycol, polybutylene glycol and the like and mixtures thereof; ethanol, 1-vinyl-2-pyrrolidone polymer (povidone) and sugar solutions of pharmaceutically acceptable lactose, dextrose (glucose), sucrose, mannose, mannitol, cyclodextrins and the like or mixtures thereof.

The pH of the oxaliplatin solution formulations of the present invention is generally in the range of about 2 to about 6, preferably in the range of about 2 to about 5, and more preferably in the range of about 3 to about 4.5.

5 The oxaliplatin solution formulations of particular interest include those described in the accompanying examples and so formulations substantially as defined in the accompanying examples are provided as a further feature of the present invention.

10 As mentioned above, oxaliplatin is a cytostatic antineoplastic agent which is useful in the therapeutic treatment of various types of susceptible cancers and tumors. Thus, the present invention also provides a method for treating cancer or a solid tumor in a mammal which comprises administering to said mammal an effective amount of an oxaliplatin solution formulation of the present invention.

15 The present invention further relates to the use of an oxaliplatin solution formulation of the present invention for the preparation of a medicament for treating cancer or a solid tumor in a mammal.

20 The present invention further relates to a method for stabilizing a solution of oxaliplatin which comprises adding an effective stabilizing amount of a buffering agent to said solution. In a preferred aspect of this method, the solution is an aqueous (water) solution and the buffering agent is oxalic acid or an alkali metal salt thereof.

25 The present invention further relates to a process for preparing the oxaliplatin solution formulations of the present invention which comprises mixing a pharmaceutically acceptable carrier, a buffering agent and oxaliplatin.

A preferred process for preparing the oxaliplatin solution formulations of the present invention comprises the steps of:

25 (a) mixing a pharmaceutically acceptable carrier and a buffering agent, preferably at about 40 °C;

- (b) dissolving oxaliplatin into said mixture, preferably at about 40 °C;
- (c) cooling the mixture resulting from step (b), preferably to about room temperature, and making up to final volume with a pharmaceutically acceptable carrier;
- 5 (d) filtering the solution from step (c); and
- (e) optionally sterilizing the product resulting from step (d).

It should be noted that while the above process can conveniently be carried out either in the presence or absence of an inert atmosphere, it is preferably carried out under an inert atmosphere, such as nitrogen.

In a particularly preferred process for preparing the oxaliplatin solution formulations 10 of the present invention the product resulting from step (d) above is sterilized by filtration or exposure to heat (terminal sterilization), preferably by exposure to heat.

The present invention further relates to a packaged pharmaceutical product comprising an oxaliplatin solution formulation of the present invention in a sealable container. The sealable container is preferably an ampoule, vial, infusion bag (pouch), or 15 syringe. If the sealable container is a syringe, the syringe is preferably a graduated syringe which allows for the measured (metered) administration of the oxaliplatin solution formulations of the present invention, and in particular allows for the measured (metered) administration of such solution formulations directly into an infusion bag.

It should also be noted that the above-described oxaliplatin solution formulations of 20 the present invention have, as is described more fully hereinbelow, been found to possess certain advantages over the presently known formulations of oxaliplatin.

Unlike the lyophilized powder form of oxaliplatin, the ready-to-use formulations of the instant invention are made by a less expensive and less complicated manufacturing process.

In addition, the formulations of the instant invention require no additional preparation or handling, e.g., reconstitution, before administration. Thus, there is no chance that an error will occur in choosing the appropriate solvent for the reconstitution as there is with a lyophilized product.

5 The formulations of the instant invention have also been found to be more stable during the manufacturing process than the previously known aqueous formulations of oxaliplatin which means that less impurities, e.g., diaquo DACH platin and diaquo DACH platin dimer, are produced in the instant formulations than in the previously known aqueous formulations of oxaliplatin.

10 The formulations of the instant invention can also be sterilized by filtration or exposure to heat (terminal sterilization) without adversely affecting the quality of the formulations.

These and other advantages of the formulations of the instant invention will become more evident upon further consideration of the instant specification and claims.

15 The formulations of the present invention are generally administered to patients, which include, but are not limited to, mammals, such as, for example, man, by conventional routes well known in the art. For example, the formulations can be administered to patients parenterally (e.g., intravenously, intraperitoneally and the like). The formulations are preferably administered parenterally and in particular are administered intravenously. When 20 infused intravenously, the formulation is generally administered over a period of up to 5 days, preferably over a period of up to 24 hours and more preferably over a period of 2 to 24 hours.

It will also be apparent to those skilled in the art that the oxaliplatin solution formulations of the present invention can be administered with other therapeutic and/or prophylactic agents and/or medicaments that are not medically incompatible therewith.

The percentage of active component, i.e., oxaliplatin, in the formulations of the present invention may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is variable depending upon the clinician's judgment using as criteria: the route of administration, the duration of treatment, the size, age and physical condition of the patient, the severity of the condition, the potency of the active component and the patient's response thereto. An effective dosage amount of the active component can thus readily be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf. In general, the active component of the formulations of the present invention can be administered to patients in doses ranging from about 10 mg/m<sup>2</sup> to 10 about 250 mg/m<sup>2</sup>, more preferably from 20 mg/m<sup>2</sup> to about 200 mg/m<sup>2</sup> and most preferably from about 30 mg/m<sup>2</sup> to about 180 mg/m<sup>2</sup>. The preferred dosing regimen for oxaliplatin includes administration of repeated dosages of oxaliplatin in cycles of 1 to 5 days at intervals of 1 to 5 weeks.

The following examples will further illustrate the invention without, however, 15 limiting it thereto. All temperatures are expressed in degrees Celsius (°C).

The formulations of Examples 1-14 set forth in Tables 1A and 1B were prepared by the following general procedure:

Dispense hot water (40 °C) for injection (W.F.I.) and bubble through with filtered nitrogen for approximately 30 minutes.

Transfer an appropriate amount of the W.F.I. required to a suitable mixing vessel while maintaining under nitrogen. Set aside the remaining W.F.I. to make up to the final volume.

Weigh appropriate buffering agent (either in the form of a solid or preferably in the form of an aqueous buffer solution of the appropriate molarity) into a suitable container and transfer to the mixing vessel (rinse container with part of the remaining W.F.I.). Mix, e.g., on

a magnetic stirrer/hotplate, for approximately 10 minutes or, if necessary, until all of the solids have dissolved, while keeping the temperature of the solution at 40 °C.

5 Weigh oxaliplatin into a suitable container and transfer to the mixing vessel (rinse container with part of the remaining hot (40 °C) W.F.I.). Mix, e.g., on a magnetic stirrer/hotplate, until all of the solids have dissolved, while keeping the temperature of the solution at 40 °C.

Allow the solution to cool to room temperature, then make up to the final volume with the remaining W.F.I.

10 Filter the solution under vacuum through a 0.22 µm filter (e.g., a millipore type GV, 47 mm diameter filter).

Fill the solution under nitrogen into suitable sterilized and sealable containers (e.g., vials or ampoules) using a filler unit, e.g., a sterile 0.2 µm disposable hydrophilic filler unit (Minisart - NML, Sartorius), with the sealable containers being purged with nitrogen before filling and the headspace being purged with nitrogen before sealing.

15 Autoclave, i.e., terminally sterilize, the solution for 15 minutes at 121 °C using, for example, an SAL (PD270) autoclave.

It should be noted that while the above process has preferably been carried out under an inert atmosphere, such as nitrogen, the formulations of the instant invention can also be conveniently prepared in the absence of such an inert atmosphere.

20

**TABLE 1A**

Ingredient	Example 1 0.00001 M sodium oxalate	Example 2 0.00005 M sodium oxalate	Example 3 0.0001 M sodium oxalate	Example 4 0.0003 M sodium oxalate	Example 5 0.0005 M sodium oxalate	Example 6 0.001 M sodium oxalate	Example 7 0.002 M sodium oxalate
Oxaliplatin	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g	5.000 g
Water for injection	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL	1000 mL
Amount sodium oxalate	1.340 mg	6.700 mg	13.40 mg	40.20 mg	67.00 mg	134.00 mg	268.00 mg

Note: The sealable containers which were utilized for the formulations of Examples 1-7 were 20 mL clear glass ampoules.

**TABLE 1B**

Ingredient	<u>Example 8</u> 0.00001 M oxalic acid	<u>Example 9</u> 0.00005 M oxalic acid	<u>Example 10</u> 0.0001 M oxalic acid	<u>Example 11</u> 0.0003 M oxalic acid	<u>Example 12</u> 0.0005 M oxalic acid	<u>Example 13</u> 0.001 M oxalic acid	<u>Example 14</u> 0.002 M oxalic acid
Oxaliplatin	5.000 g	5.000 g	5.000 g				
Water for injection	1000 mL	1000 mL	1000 mL				
Amount Oxalic Acid*	1.260 mg	6.300 mg	12.60 mg	37.80 mg	63.00 mg	126.10 mg	252.10 mg

Note: The sealable containers which were utilized for the formulations of Examples 8-14 were 20 mL clear glass ampoules.

\* Oxalic acid is added as the dihydrate; the weights shown here are of oxalic acid dihydrate added.

The formulations of Examples 15 and 16 set forth in Table 1C were prepared in a manner similar to that described above for the preparation of the formulations of Examples 1-14.

**TABLE 1C**

Ingredient	<u>Example 15</u> 0.0002 M oxalic acid	<u>Example 16</u> 0.0004 M oxalic acid
Oxaliplatin	7.500 g	7.500 g
Water for injection	1500 mL	1500 mL
Amount Oxalic Acid*	37.82 mg	75.64 mg

10 Note: The sealable containers which were utilized for the formulations of Examples 15-16 were 20 mL clear glass ampoules.

\* Oxalic acid is added as the dihydrate; the weights shown here are of oxalic acid dihydrate added.

The formulation of Example 17 set forth in Table 1D was prepared in a manner similar to that described above for the preparation of the formulations of Examples 1-14, except that: (a) the solution was filled into the sealable containers in the absence of nitrogen (i.e., in the presence of oxygen); (b) the sealable containers were not purged with nitrogen before filling; (c) the headspace was not purged with nitrogen before sealing the containers; and (d) the sealable containers were vials rather than ampoules.

TABLE 1D

Ingredient	Example 17
	0.0002 M oxalic acid
Oxaliplatin	10.000 g
Water for injection	2000 mL
Amount Oxalic Acid*	50.43 mg

Note: 1000 mL of the solution formulation of Example 17 was filled into 5 mL clear glass vials (4 mL of solution per vial) which were sealed with a West Flurotec stopper [hereinafter referred to as Example 17(a)] and the remaining 1000 mL of the solution formulation of Example 17 was filled into 5 mL clear glass vials (4 mL of solution per vial) which were sealed with a Helvoet Omniflex stopper [hereinafter referred to as Example 17(b)].

\* Oxalic acid is added as the dihydrate; the weights shown here are of oxalic acid dihydrate added.

#### Preparation of 0.0005 M Sodium Oxalate Buffer

10 Dispense greater than 2000 mL of water for injection (W.F.I.) and bubble filtered nitrogen through the water for approximately 30 minutes.

Transfer 1800 ml of the W.F.I. into a 2000 mL Schott bottle and maintain under an N<sub>2</sub> cloud. Set aside the remainder (200 mL) to make up the final volume.

15 Weigh sodium oxalate (134.00 mg) into a weighing boat and transfer into the Schott bottle (rinsing with approximately 50 mL of W.F.I.).

Stir the mixture on a magnetic stirrer/hotplate until all of the solids have dissolved.

Transfer the solution to a 2000 mL volumetric flask and make up to 2000 mL with W.F.I. and then purge the headspace of the flask with nitrogen before stoppering.

20 The various other sodium oxalate and oxalic acid buffer solutions set forth in Tables 1A, 1B, 1C and 1D were prepared following a procedure similar to that described above for the preparation of the 0.0005 M sodium oxalate buffer solution.

#### Example 18

25 For comparative purposes, an aqueous oxaliplatin formulation, such as those disclosed in Australian patent application No. 29896/95, published March 7, 1996, was prepared as follows:

Dispense greater than 1000 mL of water for injection (W.F.I.) and bubble filtered nitrogen through the solution for approximately 30 minutes. Stir on a magnetic stirrer/hotplate and heat the W.F.I. to 40 °C.

30 Transfer 800 mL of W.F.I. into a 1000 mL Schott bottle and maintain under an N<sub>2</sub> cloud. Set aside the remainder of W.F.I. (200 mL) to make up the final volume.

Weigh oxaliplatin (5.000 g) into a small glass beaker (25 mL) and transfer into a Schott bottle, rinsing the beaker with approximately 50 mL of hot W.F.I.

Stir the mixture on a magnetic stirrer/hotplate until all of the solids have dissolved, while keeping the temperature at 40 °C.

5 Allow the solution to cool to room temperature, then transfer it to a 1000 mL volumetric flask and make up the flask to 1000 mL with cool (approximately 20 °C) W.F.I.

The solution was filtered into a 1000 mL flask through a Millipore type GV, 47 mm diameter, 0.22 µm filter using a vacuum line.

10 The solution was then filled into washed and sterilized 20 mL glass ampoules using a sterile 1.2 µm disposable hydrophilic filter unit (Minisart - NML, Sartorius). The ampoules were purged with nitrogen before filling and the headspace was purged with nitrogen before sealing.

15 Twenty-three of the ampoules were kept unautoclaved [hereinafter referred to as Example 18(a)], i.e., they were not terminally sterilized, and the remaining 27 ampoules [hereinafter referred to as Example 18(b)] were autoclaved for 15 minutes at 121 °C using a SAL (PD 270) autoclave.

#### Stability Studies

In the stability studies described hereinbelow, the following chromatographic methods were utilized to evaluate the stability of the various oxaliplatin solution formulations.

20 The percentage of the platinum (IV) species, the unspecified impurities and oxaliplatin was determined by high performance liquid chromatography (HPLC) using a Hypersil™ C18 column and a mobile phase containing dilute orthophosphoric acid and acetonitrile. Under these conditions, the platinum (IV) species and oxaliplatin had retention times of approximately 4.6 and 8.3 minutes, respectively.

25 The percentage of the diaquo DACH platin and the diaquo DACH platin dimer, as well as the unspecified impurities referred to in Tables 4-8, was determined by HPLC using a Hypersil™ BDS C18 column and a mobile phase containing phosphate buffer and acetonitrile. Under these conditions, the diaquo DACH platin and diaquo DACH platin dimer had retention times of approximately 4.3 and 6.4 minutes respectively, whereas oxaliplatin 30 eluted with the solvent front.

Oxaliplatin in various aqueous buffers

5 A 2 mg/mL oxaliplatin solution in a 0.0005 M sodium oxalate buffer solution (0.0670 mg/mL of sodium oxalate) was prepared in a manner similar to that described above for the preparation of Examples 1-14 and the stability of this solution, as well as various other oxaliplatin solutions (2 mg/mL) in a range of commonly used aqueous buffer solutions, was analyzed. The results obtained when each solution was stressed for approximately one month at 40 °C are given in Table 2.

TABLE 2

Buffer	Initial Assay (% of theoretical)	Assay after ~1 month at 40 °C (% of theoretical)
0.0005M sodium oxalate	102.1	98.8
0.1M citrate, pH 3	100.4	63.6
0.1M citrate, pH 5	95.8	24.7
0.1M acetate, pH 5	100.3	76.5
0.1M tris, pH 7	80.1	1.0
0.1M tris, pH 9	22.1	0.0
0.1M glycine, pH 3	96.8	0.1
0.1M glycine, pH 9	49.7	0.0
0.1M phosphate, pH 7	98.4	19.0

10 These results demonstrate that oxaliplatin was not stable in various commonly used aqueous buffer solutions, such as citrate, acetate, tris, glycine and phosphate buffers when the solution was stressed. However, it was discovered that stable aqueous solutions of oxaliplatin can be obtained when a buffering agent, such as oxalic acid or an alkali metal salt thereof, e.g., sodium oxalate, is utilized.

Autoclaved oxaliplatin solutions in oxalate buffer

15 A 2 mg/mL oxaliplatin solution in a 0.01 M sodium oxalate buffer (1.340 mg/mL of sodium oxalate), with a sample solution pH of approximately 4, was prepared in a manner similar to that described above for the preparation of Examples 1-14. The stability results for this solution after 0, 1, 2 and 3 autoclave cycles (with each cycle lasting 15 minutes at 121° C) are summarized in Table 3.

20

TABLE 3

Number of Autoclave Cycles	Assay (mg/mL)	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Total Impurities (% w/w)
0	2.03	ND <0.01	ND <0.01	0.02	0.02
1 (15 min/121°C)	1.96	ND <0.01	ND <0.01	0.06	0.05
2 (30 min/121°C)	2.01	ND <0.01	ND <0.01	0.09	0.10
3 (45 min/121°C)	1.97	ND <0.01	ND <0.01	0.12	0.15

ND = None Detected

A 5 mg/mL oxaliplatin solution in a 0.0002 M oxalic acid buffer and a 5 mg/mL oxaliplatin solution in a 0.0004 M oxalic acid buffer were prepared, both in the presence and the absence of oxygen, in a manner similar to that described above for the preparation of Examples 1-16. The stability results for these solutions after 0, 1, 2 and 3 autoclave cycles 5 (with each cycle lasting for 15 minutes at 121°C) and three autoclave cycles of 15 minutes at 121°C and a fourth autoclave cycle lasting for 75 minutes at 121°C (total 120 minutes) are summarized in Table 3A.

**TABLE 3A**

5 mg/mL Oxaliplatin in:	Time at 121°C (min)	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Pt(IV) Species (% w/w)	Total Unspecified Impurities (% w/w)	Total Chromatographic Impurities (% w/w)
0.0002M oxalic acid manufactured under nitrogen	0	0.10	ND <0.01	ND <0.003	ND < 0.03	0.10
	15 (1 cycle)	0.13	ND <0.01	ND <0.003	T < 0.03	0.13
	30 (2 cycles)	0.10	ND <0.01	T < 0.01	T < 0.03	0.10
	45 (3 cycles)	0.10	ND <0.01	T < 0.01	T < 0.03	0.10
	120 (4 cycles)	0.09	ND <0.01	T < 0.01	T < 0.03	0.09
0.0002M oxalic acid manufactured under oxygen	0	0.14	ND <0.01	0.02	T < 0.05	0.16
	15 (1 cycle)	0.13	ND <0.01	0.01	T < 0.05	0.14
	30 (2 cycles)	0.11	ND <0.01	T < 0.01	T < 0.05	0.14
	45 (3 cycles)	0.12	ND <0.01	T < 0.01	T < 0.05	0.15
	120 (4 cycles)	0.12	ND <0.01	T < 0.01	T < 0.05	0.16
0.0004M oxalic acid manufactured under nitrogen	0	0.14	ND <0.01	T < 0.01	T < 0.05	0.14
	15 (1 cycle)	0.14	ND <0.01	T < 0.01	T < 0.05	0.14
	30 (2 cycles)	0.12	ND <0.01	T < 0.01	T < 0.05	0.12
	45 (3 cycles)	0.11	ND <0.01	T < 0.01	T < 0.05	0.11
	120 (4 cycles)	0.12	ND <0.01	T < 0.01	T < 0.05	0.12
0.0004M oxalic acid manufactured under oxygen	0	0.13	ND <0.01	0.02	ND < 0.05	0.15
	15 (1 cycle)	0.13	ND <0.01	0.01	T < 0.05	0.14
	30 (2 cycles)	0.13	ND <0.01	0.01	T < 0.05	0.14
	45 (3 cycles)	0.11	ND <0.01	0.01	T < 0.05	0.12
	120 (4 cycles)	0.11	ND <0.01	T < 0.01	T < 0.05	0.11

ND = Not detected

10 T = Trace

The above results demonstrate that the oxaliplatin solution formulations of the present invention can be terminally sterilized without adversely affecting the quality of the formulation.

**Stability studies for formulations of Examples 1-17**

15 The oxaliplatin solution formulations of Examples 1-14 were stored for up to 6 months at 40° C and the stability results of this study are summarized in Tables 4 and 5.

TABLE 4

Example No.	Sodium Oxalate Molarity	Time at 40°C	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Unspecified Impurities (% w/w)
1	0.00001	initial	5.26	0.20	0.15	0.03
	0.00001	1 month	5.25	0.21	0.15	0.13
2	0.00005	initial	5.75	0.18	0.12	0.04
	0.00005	1 month	5.32	0.16	0.11	0.12
3	0.0001	initial	5.64	0.14	0.11	0.05
	0.0001	1 month	5.33	0.14	0.08	0.11
4	0.0003	initial	5.77	0.09	0.07	0.06
	0.0003	1 month	5.74	0.10	0.07	0.10
5	0.0005	initial	5.71	0.06	0.06	0.06
	0.0005	1 month	5.68	0.08	0.05	0.08
6	0.001	initial	5.48	0.04	0.04	0.06
	0.001	1 month	5.85	0.05	0.03	0.07
7	0.002	initial	5.90	0.06	0.03	0.06
	0.002	1 month	6.02	0.03	trace <0.03	0.05

TABLE 5

Example No.	Oxalic Acid Molarity	Time at 40°C	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Unspecified Impurities (% w/w)
8	0.00001	initial	5.92	0.22	0.17	0
	0.00001	1 month	5.23	0.27	0.19	0.04
9	0.00005	initial	4.40	0.15	0.05	0
	0.00005	1 month	4.71	0.16	0.03	0.02
10	0.0001	initial	3.70	0.13	trace <0.03	0
	0.0001	1 month	4.10	0.12	ND <0.01	0.02
	0.0001	3 month	3.94	0.13	ND <0.01	trace <0.03
11	0.0001	6 month	4.17	0.13	ND <0.01	trace <0.03
	0.0003	initial	3.47	0.13	ND <0.01	0
	0.0003	1 month	3.52	0.11	ND <0.01	0.01

TABLE 5 (con't.)

Example No.	Oxalic Acid Molarity	Time at 40°C	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Unspecified Impurities (% w/w)
	0.0003	3 month	3.56	0.12	ND <0.01	trace <0.03
	0.0003	6 month	3.48	0.10	ND <0.01	trace <0.03
12	0.0005	initial	3.28	0.13	ND <0.01	0
	0.0005	1 month	3.35	0.10	ND <0.01	0.01
	0.0005	3 month	3.30	0.13	ND <0.01	trace <0.03
	0.0005	6 month	3.34	0.11	ND <0.01	trace <0.03
13	0.001	initial	3.05	0.13	ND <0.01	0
	0.001	1 month	3.02	0.11	ND <0.01	0.01
14	0.002	initial	2.85	0.14	ND <0.01	0
	0.002	1 month	2.70	0.13	ND <0.01	0.01

ND = None Detected.

The oxaliplatin solution formulations of Examples 15 and 16 were stored for up to 9 months at 25°C/60% relative humidity (RH) and 40°C/75% relative humidity (RH) and the 5 stability results of this study are summarized in Table 6.

TABLE 6

Example No.	Oxalic Acid Molarity	Time	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Total Chromatographic Impurities (% w/w)
15	0.0002	Initial	3.83	0.10	ND <0.01	ND <0.003	0.10
	0.0002	1 Month (25°C/60%RH)	3.75	0.12	ND <0.01	Trace < 0.01	0.12
	0.0002	1 Month (40°C/75%RH)	3.78	0.13	ND <0.01	Trace < 0.01	0.13
	0.0002	3 Months (25°C/60%RH)	4.13	0.10	ND <0.01	Trace < 0.01	0.10
	0.0002	3 Months (40°C/75%RH)	4.16	0.12	ND <0.01	Trace < 0.01	0.12
	0.0002	6 Months (25°C/60%RH)	3.45	0.12	ND <0.01	Trace < 0.01	0.12
	0.0002	6 Months (40°C/75%RH)	3.52	0.11	ND <0.01	Trace < 0.01	0.11

TABLE 6 (con't.)

Example No.	Oxalic Acid Molarity	Time	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Total Chromato-graphic Impurities (% w/w)
16	0.0002	9 Months (25°C/60%RH)	3.62	0.14	ND <0.01	Trace < 0.01	0.14
	0.0002	9 Months (40°C/75%RH)	3.64	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	Initial	3.45	0.10	ND <0.01	Trace < 0.01	0.10
	0.0004	1 Month (25°C/60%RH)	3.40	0.13	ND <0.01	Trace < 0.01	0.13
	0.0004	1 Month (40°C/75%RH)	3.44	0.12	ND <0.01	Trace < 0.01	0.12
	0.0004	3 Months (25°C/60%RH)	3.59	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	3 Months (40°C/75%RH)	3.71	0.12	ND <0.01	Trace < 0.01	0.12
	0.0004	6 Months (25°C/60%RH)	3.24	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	6 Months (40°C/75%RH)	3.26	0.11	ND <0.01	Trace < 0.01	0.11
	0.0004	9 Months (25°C/60%RH)	3.26	0.12	ND <0.01	Trace < 0.01	0.12
	0.0004	9 Months (40°C/75%RH)	3.31	0.12	ND <0.01	Trace < 0.01	0.12

ND = None Detected.

The oxaliplatin solution formulations of Examples 17(a) and 17(b) were stored for up to 1 month at 25°C/60% relative humidity (RH) and 40°C/75% relative humidity (RH) and the stability results of this study are summarized in Table 7.

TABLE 7

Example No.	Oxalic Acid Molarity	Time	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Platinum (IV) Species (% w/w)	Unspecified Impurities (% w/w)
17(a)	0.0002	Initial	3.81	0.13	ND <0.01	0.02	Trace <0.05
	0.0002	1 Month (25°C/60%RH)	3.82	0.12	ND <0.01	0.03	Trace <0.05
	0.0002	1 Month (40°C/75%RH)	3.79	0.13	ND <0.01	0.05	0.13
17(b)	0.0002	Initial	3.53	0.14	ND <0.01	0.03	0.05
	0.0002	1 Month (25°C/60%RH)	3.72	0.12	ND <0.01	0.07	0.16
	0.0002	1 Month (40°C/75%RH)	3.73	0.12	ND <0.01	0.09	0.07

ND = None Detected.

The results of these stability studies demonstrate that buffering agents, such as sodium oxalate and oxalic acid are extremely effective in controlling the levels of impurities, such as diaquo DACH platin and diaquo DACH platin dimer, in the solution formulations of the present invention.

5 Stability of Comparative Example 18

The unbuffered oxaliplatin solution formulation of Example 18(b) was stored for one month at 40°C and the results of this stability study are summarized in Table 8.

**TABLE 8**

Time at 40 °C	Measured pH	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)	Unspecified Impurities (% w/w)
Initial	5.47	0.27	0.16	0.04
1 Month	5.27	0.23	0.16	0.14

10 In addition three separate batches of an aseptically prepared (i.e., prepared under aseptic conditions but not autoclaved) solution product (2 mg/mL of oxaliplatin in pure water) were prepared in a manner similar to that described in Example 18(a) and the batches were stored at ambient temperature for approximately 15 months. The results of this stability study are summarized in Table 9.

**TABLE 9**

Batch No.	Temperature	Diaquo DACH Platin (% w/w)	Diaquo DACH Platin Dimer (% w/w)
A	Ambient	0.34	0.29
B	Ambient	0.36	0.28
C	Ambient	0.38	0.29

**What Is Claimed Is:**

1. A stable oxaliplatin solution formulation comprising oxaliplatin, an effective stabilizing amount of a buffering agent and a pharmaceutically acceptable carrier.
2. A formulation according to claim 1 wherein the pharmaceutically acceptable carrier is water and the buffering agent is oxalic acid or an alkali metal salt thereof.
3. A formulation according to claim 2 wherein the buffering agent is oxalic acid or sodium oxalate.
4. A formulation according to claim 3 wherein the buffering agent is oxalic acid.
5. The formulation according to any one of claims 1-4 wherein the amount of buffering agent is a molar concentration in the range of from
  - (a) about  $5 \times 10^{-5}$  M to about  $1 \times 10^{-2}$  M,
  - (b) about  $5 \times 10^{-5}$  M to about  $5 \times 10^{-3}$  M,
  - (c) about  $5 \times 10^{-5}$  M to about  $2 \times 10^{-3}$  M,
  - (d) about  $1 \times 10^{-4}$  M to about  $2 \times 10^{-3}$  M, or
  - (e) about  $1 \times 10^{-4}$  M to about  $5 \times 10^{-4}$  M.
- 15 6. A formulation according to claim 5 wherein the amount of buffering agent is a molar concentration in the range of from about  $1 \times 10^{-4}$  M to about  $5 \times 10^{-4}$  M.
7. A formulation according to claim 6 wherein the amount of buffering agent is a molar concentration of about  $2 \times 10^{-4}$  M.
- 20 8. A formulation according to claim 6 wherein the amount of buffering agent is a molar concentration of about  $4 \times 10^{-4}$  M.
9. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is from about 1 to about 7 mg/mL.
10. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is from about 1 to about 5 mg/mL.

11. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is from about 2 to about 5 mg/mL.
12. A formulation according to any one of claims 1-8 wherein the amount of oxaliplatin is about 5 mg/mL.
- 5 13. A formulation according to claim 4 wherein the amount of oxaliplatin is about 5 mg/mL and the amount of buffering agent is a molar concentration of about  $2 \times 10^{-4}$  M.
14. A formulation according to claim 4 wherein the amount of oxaliplatin is about 5 mg/mL and the amount of buffering agent is a molar concentration of about  $4 \times 10^{-4}$  M.
15. A formulation according to any of claims 1-14 for use in medicine.
- 10 16. The use of oxaliplatin in preparing a formulation according to any one of claims 1-14 for treating cancer.
17. The use of oxaliplatin in preparing a formulation according to any one of claims 1-14 for treating a solid tumor.
18. A method for treating cancer in a mammal which comprises administering to said 15 mammal an effective amount of a formulation according to any one of claims 1-14.
19. A method for treating a solid tumor in a mammal which comprises administering to said mammal an effective amount of a formulation according to any one of claims 1-14.
20. A method for stabilizing a solution of oxaliplatin which comprises adding an effective stabilizing amount of a buffering agent to said solution.
- 20 21. A method according to claim 20 wherein said solution is an aqueous solution and the buffering agent is oxalic acid or an alkali metal salt thereof.
22. A process for preparing a formulation according to any one of claims 1-14 which comprises mixing a pharmaceutically acceptable carrier, a buffering agent and oxaliplatin.
23. A process for preparing a formulation according to any one of claims 1-14 which 25 comprises the steps of:

- (a) mixing a pharmaceutically acceptable carrier and a buffering agent;
- (b) dissolving oxaliplatin into said mixture;
- (c) cooling the mixture resulting from step (b) and making up to final volume with the pharmaceutically acceptable carrier;
- 5 (d) filtering the solution resulting from step (c); and
- (e) optionally sterilizing the product resulting from step (d).

24. A process according to claim 23 wherein said process is carried out under an inert atmosphere.

25. A process according to claim 23 wherein the product resulting from step (d) is 10 sterilized by exposure to heat.

26. A packaged pharmaceutical product comprising a formulation according to any one of claims 1-14 in a sealable container.

27. A packaged pharmaceutical product according to claim 26 wherein the container is an ampoule, vial, infusion bag or syringe.

15 28. A packaged pharmaceutical product according to claim 27 wherein the container is a graduated syringe.

29. A method for the measured administration of a formulation according to any one of claims 1-14, which comprises administering said formulation from a graduated syringe.

30. The invention as substantially hereinbefore described.

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(54) Title: FORMULATIONS CONTAINING OXALIPLATIN

(57) Abstract

The invention relates to pharmaceutically stable oxaliplatin solution formulations, to the method of use thereof in the treatment of cancer tumors, to processes for the preparation of such formulations, and to a method for stabilizing solutions of oxaliplatin.

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CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00572

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K9/08 A61K47/12 A61K31/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 464 210 A (TSUMURA) 8 January 1992 (1992-01-08) claims example 9 ---	1-4, 15-30
A	EP 0 642 792 A (BRISTOL-MYERS SQUIBB) 15 March 1995 (1995-03-15) cited in the application the whole document ---	1-4, 15-30
A	WO 94 12193 A (DEBIOPHARM) 9 June 1994 (1994-06-09) cited in the application the whole document ---	1-4, 15-30 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

16 September 1999

22/09/1999

Name and mailing address of the ISA  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
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 Fax: (+31-70) 340-3016

Authorized officer

Scarpioni, U

## INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 99/00572

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 04904 A (DEBIOPHARM) 22 February 1996 (1996-02-22) cited in the application the whole document -----	1-4, 15-30

## INTERNATIONAL SEARCH REPORT

Int'l. application No.

PCT/GB 99/ 00572

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 18-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00572

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 464210	A	08-01-1992		WO 9109042 A US 5214174 A		27-06-1991 25-05-1993
EP 642792	A	15-03-1995		US 5455270 A AT 152349 T AU 685126 B AU 6898294 A CA 2128641 A CN 1118252 A CY 2021 A CZ 9401884 A DE 69402931 D DE 69402931 T DK 642792 T ES 2102743 T FI 943666 A GR 3024340 T HK 115497 A HU 75154 A JP 7053368 A NO 942944 A NZ 264210 A PL 304601 A ZA 9406007 A		03-10-1995 15-05-1997 15-01-1998 23-02-1995 12-02-1995 13-03-1996 20-02-1998 15-02-1995 05-06-1997 18-12-1997 20-10-1997 01-08-1997 12-02-1995 31-10-1997 29-08-1997 28-04-1997 28-02-1995 13-02-1995 26-10-1995 20-02-1995 10-02-1995
WO 9412193	A	09-06-1994		AU 5416394 A		22-06-1994
WO 9604904	A	22-02-1996		AU 2989695 A BR 9508554 A CA 2196922 A CZ 9700379 A EP 0774963 A JP 10508289 T US 5716988 A		07-03-1996 25-11-1997 22-02-1996 11-06-1997 28-05-1997 18-08-1998 10-02-1998